PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H3191 PCT S3	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/14851	International filing date *(day/month/year)* 23.12.2003	Priority date *(day/month/year)* 23.12.2003
International Patent Classification (IPC) or both national classification and IPC INV. A61K7/48 A61P17/00 A61K35/78		
Applicant CLR CHEMISCHES LABORATORIUM DR. KURT RICHTER GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.10.2004	08.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hauss, R Telephone No. +49 89 2399-8056

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/14851

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-20 as originally filed

Claims, Numbers

1-26 received on 18.02.2005 with letter of 17.02.2005

Drawings, Sheets

1/2, 2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1, 3

   because:

   ☒ the said international application, or the said claims Nos. 1, 3 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	2, 12, 15, 16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2, 12, 13, 15, 16
Industrial applicability (IA)	Yes:	Claims	2, 12, 13, 15, 16
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The present application provides compositions which are useful for the depigmentation of the human skin, for cosmetic as well as for therapeutic purposes (p. 2, par. 2; p. 3, par. 3 - p. 4 / bottom of page; cl. 2-3).

   Hence, claims 1, 3 and dependent claims 5-11 and 17-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated under Article 33(1) PCT with respect to novelty, inventive activity or the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. For the assessment of the present claims 1, 3, 5-11, 17-20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. The following documents (D1-D6) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1: XP002293222 & JP-A-07 025762
   D2: XP002293178 & RU2038070 C1
   D3: DE 42 06 233 C1 cited in the application
   D4: DE-A- 43 18 280
   D5: WO-A-99 52536
   D6: XP00903565

4. The present application does not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 2, 12, 15 and 16 is not new in the sense of Article 33(2) PCT.

4.1 Documents D1-D6 disclose extracts of *Bellis perennis* obtained with polar extraction solvents such as water or water/alcohol mixtures (cf. D1: ex. 7; D2: abstract, D3: ex. 1-3; D4: ex. 1-2; D5: ex. 1; D6: p. 111).
The subject-matter of claim 12 lacks novelty over D1, D2 and D5.
The extraction process as defined in amended claim 13 using glycols, glycol/water mixtures or aqueous buffers as extraction solvents is novel over the disclosure of D1-D6. However, there is no evidence showing that the extracts obtainable according to the process of claim 13 differ in any of their technical features from the extracts described in the prior art. Hence, the subject-matter of claims 15 and 16 lacks novelty (Art. 33(2) PCT).

4.2 Claim 2 is directed to the use of an extract of *Bellis perennis L.* for the preparation of a pharmaceutical composition for treating or preventing acquired or inherent hyperpigmentation.
Documents D1 and D2 disclose the use of an extract of *Bellis perennis* in products which provide skin whitening activity, e.g. for treating freckles, spots, chloasma, pimply rash or ecchymosis (D1: abstract; claim 1, ex. 7, par. [0007],[0008],[0025] [0058],[0059]; D2: abstract). Hence, claim 2 lacks novelty over the disclosure of D1 and D2 (Article 33(2) PCT).
It should be noted that present claim 2 does not specify that the extract of *Bellis perennis* is used as a pharmacologically active agent for the preparation of a pharmaceutical composition for treating or preventing acquired or inherent hyperpigmentation. Any prior disclosure describing the use of said extract, in any function, in a pharmaceutical composition for treating hyperpigmentation is therefore novelty-destroying. It would furthermore appear that *Bellis perennis* extract is in fact employed, according to the teaching of D1 and D2, as one of a mixture of pharmacologically active agents.

5. The subject-matter of claim 13 lacks inventive activity (Art. 33(1) and (33) PCT), as glycols are suggested as suitable extraction solvents in the prior art (cf. D4: col. 1, ll. 55-60; D5: p. 4, ll. 8-15), and there is no evidence to show that the use of an aqueous buffer instead of water provides any technical advantages. The extraction solvents

used according to the process of claim 13 are thus regarded as obvious alternatives.

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17. Feb. 2005

Amended claims

1. Use of an extract of *Bellis perennis L.* for the depigmentation of human skin.

2. Use of an extract of *Bellis perennis L.* for the preparation of a pharmaceutical composition for treating or preventing aquired or inherent hyperpigmentation.

3. Method for depigmentation of human skin comprising the application of a cosmetic composition to said skin, wherein said composition comprises a depigmenting effective amount of an extract of *Bellis perennis L.*.

4. Use as defined in claim 2, wherein the composition is a cream, an ointment, an emulsion (milk), a tonic (lotion), stick, dispersion, a formulation comprising a tenside, a solution or a gel.

5. Use according to any one of claims 1, 2 or 4, wherein the composition comprises at least one additional depigmentation agent, anti-inflammatory agent or antioxidant.

6. Use according to any of claims 1, 2, 4 or 5, wherein the composition comprises between 1% (w/w) and 10% (w/w), more preferable between 2% (w/w) and 5% (w/w), and most preferable

3% (w/w) extract of *Bellis perennis L.*.

7. Use according to any one of claims 1-2 or 5-6 for the prevention, treatment or amelioration of hyperpigmentation selected from pigmented spots, lentigo senilis, freckles, ephelides, post inflammatory hyperpigmentation, pigmented keratosis, melasma and chloasma and hypopigmentation selected from vitiligo, piebaldism and leucoderma due to cicatrisation.

8. Method as defined in claim 3, wherein the composition is a cream, an ointment, an emulsion (milk), a tonic (lotion), stick, dispersion, a formulation comprising a tenside, a solution or a gel.

9. Method according to claim 3 or 8, wherein the composition comprises at least one additional depigmentation agent, anti-inflammatory agent or antioxidant.

10. Method according to any of claims 3, 8 or 9, wherein the composition comprises between 1% (w/w) and 10% (w/w), more preferable between 2% (w/w) and 5% (w/w), and most preferable 3% (w/w) extract of *Bellis perennis L.*.

11. Method according to any one of claims 3, 9 or 10 for the prevention, treatment or amelioration of hyperpigmentation selected from pigmented spots, lentigo senilis, freckles, ephelides, post inflammatory hyperpigmentation, pigmented deratosis, melasma and chloasma and hypopigmentation selected from vitiligo, piebaldism and leucoderma due to

cicatrisation.

12. Composition as defined in any of claims 1-11, wherein the composition comprises between 1% (w/w) and 10% (w/w), more preferable between 2% (w/w) and 5% (w/w), and most preferable 3% (w/w) extract of *Bellis perennis L.*.

13. Process for the preparation of an extract of *Bellis perennis L.* comprising, maceration, percolation, decoction, soxleth extraction or digestion with an extraction medium selected from glycols and glycol water mixtures and aqueous buffers selected from Dulbecco`s phosphate buffer pH 7.2 (containing 8000 mg sodium chloride, 2000 mg potassium chloride, 1150 mg disodium hydrogenphosphate, 200 mg dipotassium phosphate per liter), or Sörensen phosphate buffer having a pH between about 5.0 and 8.0, preferably pH 5.0 (containing 0.06M potassium phosphate and 0.06M disodium phosphate) or citric acid buffers preferably selected from Sörensen citrate buffer, having a pH between about 1.2 and 5.0, preferably pH 3.0 (containing 0.1M sodium citrate and 0.1M HCl), preferably at elevated temperatures.

14. Process according to claim 13, whereby the process comprises decoction with a buffer selected from Dulbecco`s phosphate buffer pH 7.2, Sörensen phosphate buffer pH 5.0 and Sörensen citrate buffer pH 3 at elevated temperatures, preferably at 100°C for 1h.

15. Extract of *Bellis perennis L.* obtainable by the process according to claim 13 or 14.

16. Cosmetic or pharmaceutical composition comprising an extract of *Bellis perennis L.* according to claim 15.

17. Use of any of claims 1, 2, 4, 5, 6, or 7, wherein the extract is prepared from fresh or dried plant material.

18. Use of any of claims 1, 2, 4, 5, 6, 7 or 17, wherein the extract is prepared from the whole plant or the flower heads of *Bellis perennis L.*.

19. Method according to claims 3, 8, 9, 10 or 11, wherein the extract is prepared from fresh or dried plant material.

20. Method according to claims 3, 8, 9, 10, 11 or 19, wherein the extract is prepared from the whole plant or the flower heads of *Bellis perennis L.*.

21. Composition according to claims 12 or 16, wherein the extract is prepared from fresh or dried plant material.

22. Composition according to claims 12, 16 or 21, wherein the extract is prepared from the whole plant or the flower heads of *Bellis perennis L.*.

23. Process according to claims 13 or 14, wherein the extract is prepared from fresh or dried plant material.

24. Process according to claims 13, 14 or 23, wherein the extract is prepared from the whole plant or the flower heads of *Bellis perennis L.*.

25. Extract according to claim 15, wherein the extract is prepared from fresh or dried plant material.

26. Extract according to claim 15 or 25, wherein the extract is prepared from the whole plant or the flower heads of *Bellis perennis L.*.